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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/711,724	11/13/2000	Clifford Tabin	HMSU-P14-006	7675
28120	7590	12/23/2004	EXAMINER	
ROPES & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			HOWARD, ZACHARY C	
			ART UNIT	PAPER NUMBER

1646

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/711,724

Applicant(s)

TABIN ET AL.

Examiner

Zachary C Howard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 10/4/04.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

4) ☒ Claim(s) 1,3,6,7,17,20-22,27,29,30,32-36,42-44,47-49,63,64,66-73,78,81-83,92 and 93 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

- 5) ☒ Claim(s) 1,3,7 is/are allowed.
- 6) ☒ Claim(s) 6,17,20-22,27,29,30,32-36,42-44,47-49,63,64,66-73,78,81-83,92 and 93 is/are rejected.
- 7) ☐ Claim(s) 6 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Applicant's amendments filed 10/04/2004 are acknowledged. Claims 23, 26, 45-46, 65, 74-76 and 84 are canceled. Claims 1, 3, 6-7, 17, 20-22, 27, 29-30, 33-34, 47-49, 63-64, 68-70, 71-73, 78, and 81-83 have been amended. Newly presented claims 92 and 93 are added. Claims 1, 3, 6-7, 17, 20-22, 27, 29-30, 32-36, 42-44, 47-49, 63-64, 66-67, 68-73, 78, 81-83 and 92-93 are under consideration.

This Office Action is in response to applicant's arguments, filed 10/04/2004.

2. Applicant's amendment to the specification to provide a more descriptive title is acknowledged, and the objection to the title is withdrawn. It is noted, however, that in the newly submitted title "Screening assays for Agonists and Antagonist of the Hedgehog Signaling Pathway" should properly read "Antagonists".

### ***Claim Objections***

3. Applicant's amendments to claims 34, 47-49 and 68-69 are acknowledged and the objections to these claims are withdrawn.

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The amendment to claim 6

has made this claim dependent on claim 17. However, the amendments to claim 6 and 17 have made claim 6 identical to part (c) of claim 17. Therefore, claim 6 does not further limit claim 17.

***Claim Rejections - 35 USC § 112***

4. Claims 6, 17, 20-22, 27, 29-30, 32-36, 42-44, 47-49, 63-64, 66-73, 78, 81-83, and 92-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6, 17, 20, 30, 33, 63, and 78 have been amended to include genes controlled by a GLI transcriptional regulatory element. New claim 92 also includes this limitation. Applicants submit that the GLI transcriptional regulatory sequence is described sufficiently in the specification (on page 64 to 66) to indicate Applicants were in possession of the invention of the invention at the time of filing and satisfying the written description guidelines. The sole teaching of the specification that GLI gene transcription responds to the hedgehog protein is located on page 64, lines 26-29, which read "Transcription of the GLI gene has been reported to be upregulated in response to hedgehog in limb buds, while transcription of the GLI3 gene is downregulated in response to hedgehog induction (Marigo et al. (1996) Development 122: 1225-1233)." This teaching first appeared in the priority application of 08/674509,

filed 7/02/1996. The cited Marigo reference (in which 4 of the 5 authors are the Applicants) does not appear to contain any teachings regarding or any reference to the GLI gene. The transcriptional regulatory regions required for expression of GLI and GLI3 are not taught in Marigo, or in the specification.

The examiner maintains that the specification does not sufficiently describe any GLI transcriptional regulatory sequence to meet the written description guidelines. The specification would not reasonably convey to one skilled in the art that the inventor(s) had possession of GLI transcriptional regulatory sequences. The written description issue is not whether the specification enables one of skill in the art to perform further experimentation to make the GLI transcriptional regulatory sequences, but whether the inventor actually had possession of them.

Applicants argue that at the time of the invention that the concept of regulatory sequences was known in the art. This argument has been fully considered, but is not found persuasive because the general concept of regulatory sequences does not teach possession of specific regulatory sequences of the GLI gene promoter necessary to make a reporter gene construct responsive to hedgehog pathway signaling. The concept only provides a skilled artisan with general guidelines to follow to perform further experimentation to determine if the transcriptional regulatory sequences responsive to the hedgehog pathway exist, and if so, what they are. In order to possess the GLI transcriptional regulatory regions, a skilled artisan would need use a GLI gene probe to isolate genomic DNA covering the 5' flanking region and the coding region of the human GLI gene. One would then need to functionally analyze the 5' flanking region

of the GLI gene to identify if there actually is or is not any region that is responsive to hedgehog. For example, the regulation of GLI mRNA expression could be due to regulation of the rate of mRNA turnover rather than due to a transcriptional regulatory region.

Applicant argues that identification and sequencing of the distinct negative regulatory region or regions is not necessary to practice the claimed invention, as long as the negative regulatory elements are present somewhere within the constructs used to carry out the methods. Applicant further argues that individual regulatory elements need not be isolated from the remainder of the non-coding region to function. This argument has been fully considered but is not found persuasive. The examiner agrees that the full sequencing of the regions is not necessary to practice the claimed invention. However, some sort of identification of a region or regions to include in a reporter gene construct is necessary. At the minimum, a specific DNA fragment from the non-coding region containing the regulatory region is necessary in order to make the constructs envisioned by the Applicant. Applicant has not even provided an outer limit to the non-coding region and therefore it could potentially be anywhere in the entire genome.

For these reasons, it is maintained that the skilled artisan would not have understood the inventor to be in possession of the transcriptional regulatory elements of the GLI gene that are responsive to hedgehog pathway.

5. Claims 6, 17, 20-22, 27, 29-30, 32-36, 42-44, 47-49, 63-64, 66-73, 78, 81-83, and 92-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with

the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6, 17, 20, 30, 33, 63, and 78 have been amended to include reporter genes controlled by a GLI transcriptional regulatory element. New claim 92 also includes this limitation.

Applicants submit that the enablement rejection was made on grounds parallel to the written description rejection and submit that the arguments submitted with respect to the lack of written description adequately address the enablement rejection. This argument has been fully considered, but is not found persuasive. As described above, the examiner has maintained the written description rejection, and submits that this lack of written description prevents one of skill in the art from making and using the invention for the reasons parallel to those described above.

6. Claims 78 and 81-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 78 was previously rejected as indefinite because it is drawn to an assay to "identify agents that antagonize a bioactivity of a hedgehog protein" and it was unclear if the hedgehog protein was present in the assay, because the claim read "hedgehog receptor" (which could mean a protein that binds hedgehog, such as patched). Applicant has amended "hedgehog receptor" to read "patched protein binds a naturally occurring

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hedgehog protein". While this amendment removes the indefinite term "hedgehog receptor", claim 78 is still indefinite because it is now unclear how the method steps, which do not include the hedgehog protein will identify an agent that antagonizes a bioactivity of a hedgehog protein. It is suggested that applicant either amend the preamble of the claim to read "...agents that antagonize the hedgehog pathway." (as in claim 30) or include a comparison step to the induction of a response in the presence of the hedgehog protein (as in claims 63 and 92).

The remaining claims are rejected under 35 U.S.C § 112 for being dependent on an indefinite claim.

#### ***Claim Rejections - 35 USC § 102***

7. Applicant's arguments have been fully considered and are persuasive. All of the amended claims are directed to screening methods in which the GLI expression or GLI reporter construct are examined. The cited references, Scott et al #1 and Scott et al #2, does not teach use of the GLI gene to detect activation of the hedgehog pathway.

Therefore, the 102(e) rejection of the above claims has been withdrawn.

#### ***Conclusion***

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37

CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

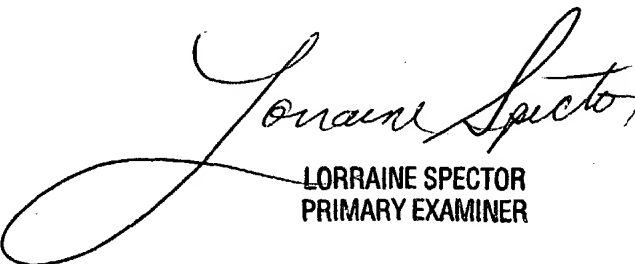
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:00 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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